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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,088	06/15/2006	Marie-Philippe Biron	P71338US0	1568

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WASHINGTON, DC 20004

EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
10/15/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/583,088	BIRON, MARIE-PHILIPPE	
	Examiner	Art Unit	
	TERESA E. STRZELECKA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-66* is/are pending in the application.

4a) Of the above claim(s) *32-35,41,42,47,49,52,57,59,64 and 66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-31,36-40,43-46,48,50,51,53-56,58,60-63 and 65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed July 17, 2009. Claims 1-26 were previously pending, with claims 4-7, 12, 21 and 26 withdrawn from consideration. Applicant cancelled claims 1-26 and added new claims 27-66. The new claims will be considered with respect to previously elected SEQ ID NO: 2, 3 and 8.

2. Newly submitted claims 32-35, 41, 42, 47, 49, 52, 57, 59, 64 and 66 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: these claims contain SEQ ID NO: 2, 3 and 8, which were not previously elected for examination.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 32-35, 41, 42, 47, 49, 52, 57, 59, 64 and 66 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

3. Applicant's claim cancellations obviated all of the previously presented rejections and objections. Claims 27-21, 36-40, 43-46, 48, 50, 51, 53-56, 58, 60-63 and 65 will be examined.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 does not contain a SEQ ID NO for the oligonucleotide sequence.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 27-29, 31, 36, 43 and 45 are rejected under 35 U.S.C. 102(e) as being anticipated by Morrissey et al. (US 2003/0206887 A1; filed September 16, 2002).

Regarding claims 27 and 29, Morrissey et al. teach sequences comprising SEQ ID NO: 2 and 3 (see sequence search results below) (SEQ ID NO: 919, 931 and 1303; Table II).

```
US-10-244-647-919/c
; Sequence 919, Application US/10244647
; Publication No. US20030206887A1
; GENERAL INFORMATION:
;  APPLICANT: Ribozyme Pharmaceutical, Inc.
;  APPLICANT:  Morrissey, David
;  APPLICANT:  McSwiggen, James
;  APPLICANT:  Beigelman, Leonid
;  TITLE OF INVENTION: RNA Interference Mediated Inhibition of Hepatitis B Virus
(HBV) Using
;  TITLE OF INVENTION:  Short Interfering Nucleic Acid (siNA)
;  FILE REFERENCE: 400/060 (MBHB02-1000)
;  CURRENT APPLICATION NUMBER: US/10/244,647
;  CURRENT FILING DATE:  2003-04-14
;  PRIOR APPLICATION NUMBER: US 60/358,580
;  PRIOR FILING DATE: 2002-02-20
;  PRIOR APPLICATION NUMBER: US 60/393,924
;  PRIOR FILING DATE: 2002-07-03
;  PRIOR APPLICATION NUMBER: PCT US02/09187
;  PRIOR FILING DATE: 2002-03-26
;  PRIOR APPLICATION NUMBER: US 60/296,876
;  PRIOR FILING DATE: 2001-06-08
;  NUMBER OF SEQ ID NOS: 1524
;  SOFTWARE: PatentIn version 3.0
; SEQ ID NO 919
;   LENGTH: 19
;   TYPE: RNA
;   ORGANISM: Artificial Sequence
;   FEATURE:
```

```
;   OTHER INFORMATION: Description of Artificial Sequence:  siNA antisense
region
US-10-244-647-919

  Query Match             100.0%;  Score 18;  DB 8;  Length 19;
  Best Local Similarity   100.0%;  Pred. No. 80;
  Matches   18;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GCTGAATCCCGCGGACGA 18
              ||||||||||||||||||
Db         19 GCTGAATCCCGCGGACGA 2


RESULT 5
US-10-244-647-931/c
; Sequence 931, Application US/10244647
; Publication No. US20030206887A1
; GENERAL INFORMATION:
;  APPLICANT: Ribozyme Pharmaceutical, Inc.
;  APPLICANT:  Morrissey, David
;  APPLICANT:  McSwiggen, James
;  APPLICANT:  Beigelman, Leonid
;  TITLE OF INVENTION: RNA Interference Mediated Inhibition of Hepatitis B Virus
(HBV) Using
;  TITLE OF INVENTION:  Short Interfering Nucleic Acid (siNA)
;  FILE REFERENCE: 400/060 (MBHB02-1000)
;  CURRENT APPLICATION NUMBER: US/10/244,647
;  CURRENT FILING DATE:  2003-04-14
;  PRIOR APPLICATION NUMBER: US 60/358,580
;  PRIOR FILING DATE: 2002-02-20
;  PRIOR APPLICATION NUMBER: US 60/393,924
;  PRIOR FILING DATE: 2002-07-03
;  PRIOR APPLICATION NUMBER: PCT US02/09187
;  PRIOR FILING DATE: 2002-03-26
;  PRIOR APPLICATION NUMBER: US 60/296,876
;  PRIOR FILING DATE: 2001-06-08
;  NUMBER OF SEQ ID NOS: 1524
;  SOFTWARE: PatentIn version 3.0
; SEQ ID NO 931
;   LENGTH: 19
;   TYPE: RNA
;   ORGANISM: Artificial Sequence
;   FEATURE:
;   OTHER INFORMATION: Description of Artificial Sequence:  siNA antisense
region
US-10-244-647-931

  Query Match             100.0%;  Score 18;  DB 8;  Length 19;
  Best Local Similarity   100.0%;  Pred. No. 80;
  Matches   18;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GCTGAATCCCGCGGACGA 18
              ||||||||||||||||||
Db         18 GCTGAATCCCGCGGACGA 1
```

```
RESULT 3
US-10-244-647-1303/c
; Sequence 1303, Application US/10244647
; Publication No. US20030206887A1
; GENERAL INFORMATION:
;  APPLICANT: Ribozyme Pharmaceutical, Inc.
;  APPLICANT:  Morrissey, David
;  APPLICANT:  McSwiggen, James
;  APPLICANT:  Beigelman, Leonid
;  TITLE OF INVENTION: RNA Interference Mediated Inhibition of Hepatitis B Virus
(HBV) Using
;  TITLE OF INVENTION:  Short Interfering Nucleic Acid (siNA)
;  FILE REFERENCE: 400/060 (MBHB02-1000)
;  CURRENT APPLICATION NUMBER: US/10/244,647
;  CURRENT FILING DATE:  2003-04-14
;  PRIOR APPLICATION NUMBER: US 60/358,580
;  PRIOR FILING DATE: 2002-02-20
;  PRIOR APPLICATION NUMBER: US 60/393,924
;  PRIOR FILING DATE: 2002-07-03
;  PRIOR APPLICATION NUMBER: PCT US02/09187
;  PRIOR FILING DATE: 2002-03-26
;  PRIOR APPLICATION NUMBER: US 60/296,876
;  PRIOR FILING DATE: 2001-06-08
;  NUMBER OF SEQ ID NOS: 1524
;  SOFTWARE: PatentIn version 3.0
; SEQ ID NO 1303
;   LENGTH: 23
;   TYPE: RNA
;   ORGANISM: Hepatitis B virus
US-10-244-647-1303

  Query Match             100.0%;  Score 21;  DB 8;  Length 23;
  Best Local Similarity   100.0%;  Pred. No. 14;
  Matches   21;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GTGCAGAGGTGAAGCGAAGTG 21
              |||||||||||||||||||||
Db         21 GTGCAGAGGTGAAGCGAAGTG 1
```

Regarding claims 28 and 31, Morrissey et al. teach a sequence consisting of SEQ ID NO: 3 (SEQ ID NO: 1380, Table III):

```
US-10-244-647-1380
; Sequence 1380, Application US/10244647
; Publication No. US20030206887A1
; GENERAL INFORMATION:
;  APPLICANT: Ribozyme Pharmaceutical, Inc.
;  APPLICANT:  Morrissey, David
;  APPLICANT:  McSwiggen, James
;  APPLICANT:  Beigelman, Leonid
;  TITLE OF INVENTION: RNA Interference Mediated Inhibition of Hepatitis B Virus
(HBV) Using
```

```
;  TITLE OF INVENTION:  Short Interfering Nucleic Acid (siNA)
;  FILE REFERENCE: 400/060 (MBHB02-1000)
;  CURRENT APPLICATION NUMBER: US/10/244,647
;  CURRENT FILING DATE:  2003-04-14
;  PRIOR APPLICATION NUMBER: US 60/358,580
;  PRIOR FILING DATE: 2002-02-20
;  PRIOR APPLICATION NUMBER: US 60/393,924
;  PRIOR FILING DATE: 2002-07-03
;  PRIOR APPLICATION NUMBER: PCT US02/09187
;  PRIOR FILING DATE: 2002-03-26
;  PRIOR APPLICATION NUMBER: US 60/296,876
;  PRIOR FILING DATE: 2001-06-08
;  NUMBER OF SEQ ID NOS: 1524
;  SOFTWARE: PatentIn version 3.0
; SEQ ID NO 1380
;   LENGTH: 21
;   TYPE: RNA
;   ORGANISM: Artificial Sequence
;   FEATURE:
;   OTHER INFORMATION: Description of Artificial Sequence:  siNA antisense
region
US-10-244-647-1380

  Query Match             100.0%;  Score 21;  DB 8;  Length 21;
  Best Local Similarity   85.7%;  Pred. No. 14;
  Matches   18;  Conservative    3;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GTGCAGAGGTGAAGCGAAGTG 21
              |:|||||||:|||||||||:|
Db          1 GUGCAGAGGUGAAGCGAAGUG 21
```

Regarding claim 36, Morrissey et al. teach hybridizing an HBV sequence with the oligonucleotides from Tables II or III (page 5, [0040]-[0046]).

Regarding claims 43 and 45, Morrissey et al. teach using multiple siRNA sequences in the silencing reactions, which involves hybridization of the oligonucleotides with HBV mRNA (page 6, [0048]; page 14, [0111]).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary

skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 27-29, 31, 36-40, 43-46, 48, 50, 51, 53-56 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saito et al. (J. Med. Virol., vol. 58, pp. 325-331, 1999; cited in the previous office action) as evidenced by Heid et al. (Genome Res., vol. 6, pp. 986-994, 1996; cited in the previous office action) and the GenBank sequence with accession No. X98077 (1997), Higashi et al. (Liver, vol. 22, pp. 374-379, October 2002), Stoll-Becker et al. (J. Virol., vol. 71, pp. 5399-5407, 1997), Su et al. (Clin. Cancer Res., vol. 7, pp. 2005-2015, 2001) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999).

A) As a reference for further discussion, the positions of claimed SEQ ID NO: 2, 3 and 8 with respect to the HBV genome with GenBank accession No. are as follows (see BLAST alignment): SEQ ID NO: 2; bp 1440-1457; SEQ ID NO: 3: bp 1582-1602; SEQ ID NO: 8: bp 1527-1548.

Regarding claims 27-29, 31, 37-40, 43-46, 48, 50 and 51, Saito et al. teach a set of three oligonucleotides, each between 15 and 40 bp long, for the detection of the X gene of HBV (page 326, last paragraph). The position of these primers and probe are as follows with respect to the HBV wild-type genome sequence with GenBank accession No. X98077 (see BLAST alignment of these sequences): the first primer hybridizes between bp 1414-1435 of that sequence, the second primer with bp 1728-1744, and the probe with bp 1681-1705. Therefore, the amplicon produced by Saito et al. overlaps with the amplicon produced by the instant primers between bp 1440-1602, i.e., the amplicon produced using the instant primers is 100% contained within the amplicon produced by the primers of Saito et al.

Regarding claim 40, Saito et al. teach the probes were TaqMan probes according to Heid et al. (page 325, second paragraph). As evidenced by Heid et al., TaqMan probes comprise a

fluorophore and a quencher (page 987, second and third paragraph), anticipating the limitations of an oligonucleotide comprising a fluorophore and a quencher.

Regarding claim 36, Saito et al. teach the use of oligonucleotides to detect HBV (page 326, last paragraph; page 327, first paragraph); since the primers hybridize to the HBV, the method of claim 36 is anticipated.

Regarding claim 53, Saito et al. teach a method comprising:

a) contacting a set of oligonucleotides according to claim 43 with a biological sample or nucleic acid preparation obtained from a biological sample, under conditions suitable for the oligonucleotides to hybridize to a HBV nucleic acid present in the sample (page 326, last paragraph; page 327, first paragraph);

b) amplifying said HBV nucleic acid using said oligonucleotides as primers (page 326, last paragraph; page 327, first paragraph);

c) detecting the amplification product, indicative of the presence of a HBV in the biological sample (page 326, last paragraph; page 327, first paragraph).

Regarding claim 54, Saito et al. teach PCR (page 326, last paragraph).

Regarding claims 55, 56 and 58, Saito et al. teach a probe for the X gene of HBV virus (page 326, last paragraph), which hybridizes to the bp 1681-1705 of the GenBank accession No. X98077. Saito et al. teach that the probes were TaqMan probes according to Heid et al. (page 325, second paragraph). As evidenced by Heid et al., TaqMan probes comprise a fluorophore and a quencher (page 987, second and third paragraph), anticipating the limitations of an oligonucleotide comprising a fluorophore and a quencher.

B) Saito et al. do not specifically teach primers and probes 15-40 bp in length comprising or consisting of SEQ ID NO: 2, 3 or 8.

However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the known sequences of the HBV genome to design primers and probes for the detection of the genome with a high expectation of success. In *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of HBV virus, and in particular for the detection of the X protein, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

The expectation of success of using alternative primers derived from the sequence is provided by the references listed below.

Higashi et al. amplified HBV virus X protein by PCR using two sets of primers (page 375, paragraphs 5-9). These primers hybridize to the following regions of the X98077 sequence (see

BLAST alignment): OAL-X1: bp 1433-1455, OAL-X4: bp 1588-1610. These primers create an amplicon which is shifted 5' with respect to the instant amplicon by 7 bp.

Stoll-Becker et al. teach detection of HBV X gene by PCR using primers P1 and P2 (page 5400, sixth paragraph; Table 1), which hybridize to the following regions of the X98077 sequence (see BLAST alignment): P1: bp 1380-1401, P2: bp 1529-1550. Therefore the amplicon generated by the primers of Stoll-Becker et al. overlaps with the amplicon generated by the instant primers between bp 1440-1550.

Finally, Su et al. teach amplification of the HBV virus in circulation of infected patients by PCR using primers directed to the X gene (page 2006, paragraphs 5 and 6), txs3 and xas1. As can be seen from the alignment of the txs3 primer with the GenBank sequence X98077, the txs3 primer hybridizes to a region between bp 1561-1580, i.e., within the amplicon generated by the instant primers.

As can be seen from the above references, selection of primers from the different and overlapping regions of the X gene produced successful amplification of the HVB sequences.

Buck et al. expressly provides evidence of the equivalence of primers in support of the above conclusion regarding primer selection from a known sequence. Specifically, Buck et al. invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck et al. also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see

page 533, column 1). Buck et al. expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck et al. provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

10. Claims 60-63 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saito et al. (J. Med. Virol., vol. 58, pp. 325-331, 1999; cited in the previous office action) as evidenced by Heid et al. (Genome Res., vol. 6, pp. 986-994, 1996; cited in the previous office action) and the GenBank sequence with accession No. X98077 (1997), Higashi et al. (Liver, vol. 22, pp. 374-379, October 2002), Stoll-Becker et al. (J. Virol., vol. 71, pp. 5399-5407, 1997), Su et al. (Clin. Cancer Res., vol. 7, pp. 2005-2015, 2001), Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999), Pasupuletti et al. (U.S. Patent No. 6,635,428 B2; cited in the previous office action) and Stratagene Catalog (p. 39, 1988).

Regarding claims 60, 61, 63 and 65, Saito et al. teach a set of three oligonucleotides, two primers and a probe, each between 15 and 40 bp long, for the detection of the X gene of HBV (page 326, last paragraph). The position of these primers and probe are as follows with respect to the HBV wild-type genome sequence with GenBank accession No. X98077 (see BLAST alignment of these sequences): the first primer hybridizes between bp 1414-1435 of that sequence, the second primer with bp 1728-1744, and the probe with bp 1681-1705. Therefore, the amplicon produced by Saito et al. overlaps with the amplicon produced by the instant primers between bp 1440-1602, i.e., the

amplicon produced using the instant primers is 100% contained within the amplicon produced by the primers of Saito et al.

Regarding claims 63 and 65, Saito et al. teach the probes were TaqMan probes according to Heid et al. (page 325, second paragraph). As evidenced by Heid et al., TaqMan probes comprise a fluorophore and a quencher (page 987, second and third paragraph), anticipating the limitations of an oligonucleotide being detectably labeled.

Regarding claim 62, Saito et al. teach PCR (page 326, last paragraph).

B) Saito et al. do not specifically teach primers and probes 15-40 bp in length comprising or consisting of SEQ ID NO: 2, 3 or 8.

However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the known sequences of the HBV genome to design primers and probes for the detection of the genome with a high expectation of success. In *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of HBV virus, and in particular for the detection of the X protein, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed

primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

The expectation of success of using alternative primers derived from the sequence is provided by the references listed below.

Higashi et al. amplified HBV virus X protein by PCR using two sets of primers (page 375, paragraphs 5-9). These primers hybridize to the following regions of the X98077 sequence (see BLAST alignment): OAL-X1: bp 1433-1455, OAL-X4: bp 1588-1610. These primers create an amplicon which is shifted 5' with respect to the instant amplicon by 7 bp.

Stoll-Becker et al. teach detection of HBV X gene by PCR using primers P1 and P2 (page 5400, sixth paragraph; Table 1), which hybridize to the following regions of the X98077 sequence (see BLAST alignment): P1: bp 1380-1401, P2: bp 1529-1550. Therefore the amplicon generated by the primers of Stoll-Becker et al. overlaps with the amplicon generated by the instant primers between bp 1440-1550.

Finally, Su et al. teach amplification of the HBV virus in circulation of infected patients by PCR using primers directed to the X gene (page 2006, paragraphs 5 and 6), txs3 and xas1. As can be seen from the alignment of the txs3 primer with the GenBank sequence X98077, the txs3 primer hybridizes to a region between bp 1561-1580, i.e., within the amplicon generated by the instant primers.

As can be seen from the above references, selection of primers from the different and overlapping regions of the X gene produced successful amplification of the HVB sequences.

Buck et al. expressly provides evidence of the equivalence of primers in support of the above conclusion regarding primer selection from a known sequence. Specifically, Buck et al.

invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck et al. also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck et al. expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck et al. provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

C) None of the above references teaches kits.

D) Regarding claims 60-63 and 65 Pasupuletti et al. teach kits for the PCR detection of HBV in real-time (col. 5, lines 64-67; col. 6, lines 1-9).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to package the primers and probes for the detection of HBV by the methods of Saito et al., Higashi et al., Stoll-Becker et al., Su et al. and Buck et al. as suggested by Pasupuletti et al. Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10

different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control" (page 39, column 1).

11. No claims are allowed.

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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